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Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies☆

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ABSTRACT

Purpose: Temporal lobe epilepsy with antibodies (abs) against the glutamic acid decarboxylase 65 isoform (GAD-TLE) is known as an immune-mediated neurological syndrome. Here we evaluate the therapy response to various immunotherapies and epilepsy surgery in this syndrome.
Method: All patients with GAD-TLE and follow-up data and stored serum and CSF samples, identified and treated at the Bonn centre from 2002 to 2010, were studied retrospectively. Seizure freedom for ≥1 year and reduction of ≥50%, i.e. therapy response, were assessed. GAD-ab titres and neuropsychological performances were documented prior and after individual interventions.
Results: Thirteen patients with GAD-TLE were identified with the following seizure responses: corticosteroids (5 responders out of 11 treated patients); i.v. immunoglobulins (1/5), apheresis therapy (1/8); and natalizumab (1/1), selective amygdala-hippocampectomy (2/3). None of the patients achieved sustained seizure freedom apart from one patient. This patient was on antiepileptic drug treatment after discontinuation of immunotherapy.
Conclusion: The seizure response to immunotherapies in patients with GAD-TLE was poor. Corticosteroids were the most effective regarding seizure response. Especially the poor effects of apheresis therapies support the idea that GAD-abs are not directly pathogenic. None of three patients was seizure-free after temporal lobe surgery suggesting that GAD-TLE patients respond worse than others to this type of intervention. Our results reflect the chronic course of the disease with low likelihood for patients with GAD-TLE to attain long-term seizure freedom.

1. Introduction

Glutamic acid decarboxylase (GAD) catalyzes the synthesis of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Antibodies (abs) against the GAD65 isoform are markers for insulin dependent diabetes mellitus and – if present at high titres – immune-mediated neurological syndromes such as stiff-person-syndrome [1], cerebellar ataxia [2], as well as limbic encephalitis (LE) and temporal lobe epilepsy (TLE) in adults [3–5] and children [6,7]. "Subacute" LE with GAD-abs and "chronic" TLE with GAD-abs have been suggested to be two ends of one spectrum of an immune-mediated mediotemporal lobe disorder. A plausible explanation for these two "poles" is that in early stages the condition appears as "LE" and later on as chronic epilepsy [8]. To overcome terminological inconsistencies, here we use the term "immune-mediated temporal lobe epilepsy with GAD-abs" (GAD-TLE) irrespective of disease duration and "acuity". Symptoms consist of temporal lobe seizures, memory and mood disturbances.

In our former publications [5,9], patients with GAD-TLE had a worse outcome than patients with abs against the voltage gated potassium channel (VGKC) complex despite similar immunotherapeutic interventions (usually monthly i.v.-methylprednisolone

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pulses in dosages of 500–1000 mg/day on 3–5 consecutive days). Because none of the patients with GAD-TLE became seizure-free, a more chronic course of the disease has been suggested. Furthermore, direct pathogenicity of GAD-abs is still discussed controversially [10–12]. One would expect that in case of direct involvement of GAD-abs in pathogenic processes, their reduction should prompt clinical improvement.

Here, we report retrospectively our single centre experience in treatment of GAD-TLE. The patients reported here have been treated a few years after the first publications of the good treatability of encephalitides with abs against the VGKC-complex [13] or the *N*-methyl-D-aspartate receptor (NMDAR) [14]. There was a great optimism that any ab associated autoimmune encephalitis – including those with GAD-abs – would respond to adequate and consequent immunological therapy. Here we evaluate the therapy response to various immunotherapies and epilepsy surgery in patients with GAD-TLE regarding seizure frequency reduction and, if available, memory outcome.

2. Methods

2.1. Study cohort

All patients with GAD-TLE with available follow-up data and with stored serum and CSF samples for ab re-testing, studied from 2002 to 2010 at the University of Bonn, Department of Epileptology, were included in this retrospective report. The diagnosis was based on clinical features of seizures of temporal semiology and evidence of high titre serum GAD-abs (>1:2000 in accordance with a previous suggestion [15]).

The ab diagnosis was made by use of indirect immunohistochemistry with confirmation through radioimmunoprecipitation (done by Angela Vincent, Oxford/UK). Abs against the other antigens available for routine testing at that time, i.e. against the VGKC complex, against the NMDAR and against onconeural antigens Hu, Ma, amphiphysin, CV2/CRMP5 were excluded. All available serum and CSF samples were re-tested for this study by cell-based assays with acetone fixed HEK cells transfected with GAD65 (Euroimmun, Luebeck/Germany, performed by CGB). The protocol for indirect immunofluorescence follows the recommendations given by Euroimmun (FA 112d-1005-1, IgG) with few modifications: the buffer was PBS (Euroimmun: PBS-Tween); the secondary system consisted of a goat-anti-human IgG (heavy and light chain) ab conjugated with DyLight 594 produced by Jackson ImmunoResearch, West Grove, PA, USA, Code No. 109-515-088 at a dilution of 1:100 (Euroimmun: goat-anti-human IgG, conjugated with fluorescein, no further information given); nuclear counterstaining with Hoechst 33342 at 1:10,000 (Euroimmun: no nuclear staining); embedding with 1,4-diazabicyclo[2.2.2]octan (Euroimmun: glycerol). The stained cells are examined using a fluorescence microscope (Leica DM 2000; Wetzlar, Germany) with excitation at 592 nm and emission filter at 616 nm for bound ab and 350/462 nm for the nuclear counterstain. An endpoint titration was done by serial dilutions in a multiple of 1:2. The titre is the concentration at which a signal is just still detectable in comparison with adjacently stained non-transfected cells. Each titration is rated by two independent investigators. If the ratings are divergent, the mean of the two ratings is recorded. The antibody index (AI, i.e., the ratio between the CSF/serum quotients of GAD-ab titres and total IgG concentrations) indicates whether antibodies are produced intrathecally. We took an AI > 4 as an indication of intrathecal production of the specific antibody [16].

Clinical and paraclinical data were obtained from the patient records. Comorbidities were evaluated both at visit 1 and last follow-up. Tumour searches were performed in all patients according to a dedicated protocol at visit 1 [17]. For brain MRIs, a dedicated epilepsy protocol [18] was used on a 3 Tesla scanner, Philips, The Netherlands (Dept. of Neuroradiology) or a 3 Tesla "Trio" scanner from Siemens, Erlangen, Germany (Life&Brain Institute). If available previous brain MRIs from other institutions were re-assessed. MRI courses were observed at visit 1 and at last available follow up to reveal changes on long-term follow up, especially newly developed hippocampal atrophies. All images were re-evaluated for this study.

Eight patients were part of our previous study [5], except from one all with extended follow-up data in the present study. Some patients were included in the study by Wagner, dealing with morphological changes on MRI without clinical data reported [19].

2.2. Therapeutic interventions

Most patients received multiple therapeutic interventions in different chronological sequences. All patients were on antiepileptic drugs, immunotherapeutic interventions and epilepsy surgery were added on this. Only one intervention was delivered in an individual patient at the same time. We analyzed the outcome of each single therapeutic intervention (regardless of the chronological order of administration in the individual patient) and grouped them as follows: corticosteroids, intravenous immunoglobulins (IVIG), apheresis techniques (plasma exchange or immunoadsorption), natalizumab, epilepsy surgery. Some patients received temporarily only antiepileptic drugs (AED) without any other intervention, therapy response in these periods were observed as well. Azathioprine (Aza) and mycophenolat-mofetil (MMF) were given as oral long-term immunosuppressants in some patients subsequent to immunotherapies or epilepsy surgery. Their use was considered as supportive treatment and not included in further analysis.

2.3. Immunotherapy regimens

Immunotherapies were delivered as off-label individual treatment attempts after obtaining informed patient consent (compassionate use).

2.3.1. Corticosteroids

They were given as monthly i.v.-methylprednisolone (MP) pulses (500–1000 mg/day on 3–5 consecutive days) or continuously *per os* with initial standard doses of 100 mg/day. The decision on therapy duration and long-term dosage was made individually. To characterize the "intensity" of each intervention, corticosteroid doses were expressed as MP-equivalent doses (prednisone or prednisolone doses were multiplied by 0.8 [20]).

2.3.2. IVIG

IVIG were given at doses of 0.4/kg body-weight/day. They were delivered in monthly pulses, initially starting with sequences of three to five doses on consecutive days and thereafter monthly single day pulses in the following. Total doses were calculated to characterize the "intensity" of each intervention.

2.3.3. Apheresis therapy

This was performed as plasmapheresis or immunoadsorption according to commonly accepted principles. In four patients immunoadsorption was combined with continuous lumbar CSF drainage over 4 days with maximal drain of 150 ml/day (a simplified version of Wollinsky's liquorpheresis or CSF-filtration [21,22]) based on the assumption that a removal of the ab-containing CSF could reduce ab load in the CNS.

2.3.4. Natalizumab

It was used similar to the therapy regimen in multiple sclerosis with monthly single day infusions of 300 mg i.v. Before initiation of